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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/288,336	08/10/94	LUCIW	P 0035.011

EXAMINER	
WOODWARD, M	

ART UNIT	PAPER NUMBER
1813	8

18N1/0615

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DATE MAILED: 06/15/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/27/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 26 & 60-80 are pending in the application.

Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-25 & 27-59 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 26 & 60-80 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The previous Office Action (Paper No. 3, April 10, 1995) is hereby incorporated by reference.

The petition for change of inventorship under 37 C.F.R. §1.48(c) (Paper No. 4, March 27, 1995) is denied as inventor Hallewell has not signed the Oath/Declaration. Applicants' arguments concerning the lack of signing by Hallewell are not persuasive as it appears that the negotiation process is ongoing. There does not appear to be substantive evidence that there has been a refusal to cooperate on the part of inventor Hallewell.

The inclusion of "Supplemental Amendment in SN 08/107377" and "Declaration of Kenneth M. Goldman" as part of an Information Disclosure Statement (Paper No. 5, March 27, 1995) is inappropriate. Nonetheless they have been considered and pages 145-148 have been inserted into the instant specification.

Claims 60-80 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 60 is unclear because the arrangement of the elements in relation to each other is unspecified. It is also unclear how a transcription regulatory region can "cause" transcription.

It is unclear in claims 64, 66, 67, 75, 79 and 80 what it means to be derived from as there is no clear relationship linking the starting and ending material so as to warrant the conclusion that one was derived from the other.

It is unclear in claim 65 whether the intron is one which is 3' to the HCMV E1 promoter or if it is any intron which is positioned 3' to the HCMV promoter.

The limitation of claims 66, 67, and 77 "constructed in the same manner" is unclear since it could refer to the process steps involved or to the genetic elements employed in the vector.

"The a" in claim 67 is confusing.

It is unclear whether the intent of claim 71 is to the deposited plasmid or to the sequences found therein which correspond to the elements recited in claim 60.

In claim 79 shouldn't it be "the" 3' end rather than "a" 3' end.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

There is no written description of the genus of expression vectors set forth in claims 60-79. The specification contains a single example of a fragment derived from HCMV which example does not set forth the individual elements of the claimed genus so as to permit construction of other members of the genus.

Claims 60-79 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 79 and 80 are to an intron proximal to the 3' end of the promoter region of the HCMV E1 gene. The specification does not provide guidance as to how to make the intron.

Nor does the specification teach how to use the intron. While the specification teaches the inclusion of the intron in larger fragment containing the enhancer-promoter there is no guidance as to how to make and use just the intron.

Claims 79 and 80 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

There is no written description of the intron as an individual entity. It is described as part of a larger construct and there is nothing in the specification to suggest that it was viewed as a separate and distinct invention as of the time of filing.

Claims 79 and 80 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The first written description of an expression vector containing the human cytomegalovirus immediate early region (HCMV E1) occurs in SN 07/138894 with a filing date of December 24, 1987.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 60, 61 and 63-72 rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Foecking et al. (1986).

These claims are directed to expression vectors containing a plurality of regulatory regions for the control of DNA replication and transcription, intervening sequences and protein coding sequences and methods of making such vectors. Claims 76 and 77 recite vectors in a product-by-process format.

Foecking et al. (1986) discloses an expression vector which contains an SV40 origin of replication, an SV40 polyadenylation site, the HCMV E1 promoter-enhancer, an SV40 splicing site, a bacterial origin of replication, an ampicillin resistance gene as a selectable marker and the chloramphenicol acetyltransferase gene as a reporter for assessment of promoter-enhancer activity.

Claims 60-80 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Chapman et al. (1991).

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the

invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claim 62 is rejected under 35 U.S.C. § 103 as being unpatentable over Foecking et al. (1986).

The limitation of claim 62 is that the insertion site for the polypeptide coding region contains a Sal I site. It is well known in the art to insert a plurality of restriction enzyme sites into linker regions so as to permit the correct orientation of the inserted sequence. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a linker containing a Sal I site in order to facilitate the correct insertion of a sequence of interest which itself contained one or more Sal I sites.

Claim 73 is rejected under 35 U.S.C. § 103 as being unpatentable over the combined teachings of Foecking et al. (1986) in view of the arts recognition of the importance of gp120 of HIV as represented by Luciw et al. (US Patent 5,156,949).

Claim 73 limits the polypeptide coding sequence inserted into the vector to at least a portion of HIV gp120.

Foecking et al. has been discussed above, however, the further motivation for employing the vector of Foecking et al. stems from their observation that the HCMV E1 enhancer-promoter appears to be stronger than other known promoters thereby favoring its transcription over that of other genes which leads to increased production of mRNA and consequently protein.

Luciw et al. is available as prior art under the provisions of 35 U.S.C. §102(e). Luciw et al. is relied upon for its teachings of the coding sequence of HIV gp 120 and the arts interest in gp120 for the analysis of viral infection, e.g. the immune response to HIV infection.

It would have been obvious to a person of ordinary skill in the art at the time the

invention was made to insert at least a portion of the coding sequence of HIV gp120 into the vector of Foecking et al. in view of the advantages of the Foecking et al. vector for expressing heterologous genes.

Claims 74 and 75 are rejected under 35 U.S.C. § 103 as being unpatentable over the combined teachings of Foecking et al. (1986) and van Zonneveld et al. (1986).

Claim 74 adds a signal sequence to the expression vector of claim 61 and claim 75 contains the further limitation that the signal sequence employed be that of human tissue plasminogen activator.

Foecking et al. has been discussed above.

van Zonneveld et al. discloses expression vectors for the expression of human tissue-type plasminogen activator and in particular demonstrates that the signal sequence is effective even with truncated coding sequences suggesting that it functions independently of, autonomously of, the downstream coding sequences. Applicants also state at page 48 of the instant specification

> In order to achieve optimal secretion of gp 160 from mammalian tissue culture cells, the 5' end of the coding sequence was modified to accept a heterologous signal sequence known to direct efficient secretion of both the homologous gene (human tissue plasminogen activator) and deletion variants of this gene. van Zonneveld et al. (1986) Proc. Natl. Acad. Sci. USA 83:4670.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a signal sequence to facilitate the secretion or membrane association of a polypeptide of interest, particularly wherein only a portion of the polypeptide of interest is being expressed, and more specifically to utilize the signal sequence element taught by van Zonnefeld et al. as it is taught to function autonomously of the coding sequences downstream from it.

Alternatively, it would have been obvious to insert the hTPA signal and coding sequences taught by van Zonnefeld et al. into the vector of Foecking et al. in order to achieve greater expression of the hTPA gene.

The following art is made of record and applicants are encouraged to consider it when

amending the instant claims.

Stinski M F; Thomsen D R; Stenberg R M; Goldstein L C , "Organization and expression of the immediate early genes of human cytomegalovirus," J Virol, (1983 Apr) 46 (1) 1-14.

The immediate early genes of human cytomegalovirus were characterized according to map location, RNA transcripts, and translation products. Three regions in the large unique component (0.709 to 0.751 map units) were transcribed in the presence of an inhibitor of protein synthesis (anisomycin). A single size class of polyadenylated mRNA, 1.95 kilobases (kb), was transcribed abundantly relative to the other size classes. The predominant 1.95-kb viral RNA was transcribed from right to left on the prototype arrangement of the viral genome and spanned a region of approximately 2.8 kb (0.739 to 0.751 map units). This mRNA codes for a 75,000-dalton protein that represents the predominant immediate early protein detected in infected cells. Immunoprecipitation of viral proteins synthesized in vitro as well as in vivo demonstrated that the predominant immediate early protein is synthesized as a protein of 75,000 daltons, but is presumably modified in vivo, resulting in a broad banding pattern ranging from 75,000 to 68,000 daltons. A different immediate early viral gene (0.732 to 0.739 map units) is transcribed from left to right at relatively low levels. The 3' ends of the above viral RNAs terminate at approximately 230 base pairs apart in the region of approximately 0.739 map units. Five RNA size classes ranging from 2.25 to 1.10 kb were detected, but the 1.75-kb and 1.40-kb RNA size classes were more abundant from this region. At least four minor proteins are coded by these mRNAs, with apparent molecular weights ranging from 56,000 to 16,500. Last, a 1.95-kb mRNA was transcribed from a third region (0.709 to 0.728 map units). This viral mRNA was present at relatively low concentration and coded for a minor protein of 68,000 daltons. Since immediate early gene expression of human cytomegalovirus is dominated by the synthesis of an mRNA from the region of 0.739 to 0.751 map units that codes for the predominant immediate early protein found in the infected cell, we hypothesize that this protein is the major regulatory protein influencing the switch from restricted to extensive transcription.

Stenberg R M; Thomsen D R; Stinski M F, "Structural analysis of the major immediate early gene of human cytomegalovirus," J Virol, (1984 Jan) 49 (1) 190-9.

The most abundant species of human cytomegalovirus (Towne) immediate early polysome-associated RNA originates from a region of ca. 2.8 kilobases (0.739 to 0.755 map units) within the XbaI-E DNA fragment. These sequences code for a 1.95-kilobase mRNA and are referred to as immediate early coding region one (M. F. Stinski, D. R. Thomsen, R. M. Stenberg, and L. C. Goldstein, J. Virol. 46:1-14, 1983). We have utilized the nuclease mapping technique of

Berk and Sharp (A. J. Berk and P. A. Sharp, Cell 12:721-732, 1977) to examine this gene in detail. Cloned fragments of human cytomegalovirus DNA, either labeled with 32P in vivo or end labeled in vitro at the 5' or 3' termini, were hybridized to immediate early polysome-associated RNA. The hybrids were treated with single-strand-specific nuclease and subjected to electrophoresis in either neutral or denaturing gels. The major transcript was shown to be a spliced molecule containing a 3' terminal exon of 1,341 nucleotides. Upstream of the major body of the mRNA are three small exon sequences of 185, 88, and 121 nucleotides. The sequence of the exons as well as the locations of the intron-exon splice junctions were determined. Based on the DNA sequence, the viral mRNA molecule has one open reading frame which begins within the second exon and extends for 491 amino acid residues. The predicted molecular weight of the polypeptide originating from this region was estimated to be 64,000. It is hypothesized that this viral gene codes for the major regulatory protein controlling transcription of the viral genome at early times. The properties of the viral gene and its protein product are discussed.

Thomsen D R; Stenberg R M; Goins W F; Stinski M F, "Promoter-regulatory region of the major immediate early gene of human cytomegalovirus," Proc Natl Acad Sci U S A, (1984 Feb) 81 (3) 659-63.

The DNA templates containing immediate early (IE) genes of human cytomegalovirus (CMV) were transcribed in vitro by using a HeLa cell extract. When IE region 1, 2, and 3 were used, transcription was detected qualitatively only from IE region 1. Transcription was detected with DNA representing IE region 2 when the IE region 1 promoter was not present. DNA sequence analysis of the upstream regulatory region of IE region 1 detected two distinct repeats of 19 and 18 nucleotides, both being repeated four times. A putative cruciform structure could form through the surrounding sequences with each 18-nucleotide repeat being located in the unpaired region. The potential secondary structure and the repeat sequences in the regulatory region of IE region 1 are presumably related to the high level of transcription of this IE gene.

Gorman C M; Moffat L F; Howard B H, "Recombinant genomes which express chloramphenicol acetyltransferase in mammalian cells," Mol Cell Biol, (1982 Sep) 2 (9) 1044-51.

We constructed a series of recombinant genomes which directed expression of the enzyme chloramphenicol acetyltransferase (CAT) in mammalian cells. The prototype recombinant in this series, pSV2-cat, consisted of the beta-lactamase gene and origin of replication from pBR322 coupled to a simian virus 40 (SV40) early transcription region into which CAT coding sequences were inserted. Readily measured levels of CAT accumulated within 48 h after the introduction of pSV2-cat DNA into African green monkey kidney CV-1 cells.

Because endogenous CAT activity is not present in CV-1 or other mammalian cells, and because rapid, sensitive assays for CAT activity are available, these recombinants provided a uniquely convenient system for monitoring the expression of foreign DNAs in tissue culture cells. To demonstrate the usefulness of this system, we constructed derivatives of pSV2-cat from which part or all of the SV40 promoter region was removed. Deletion of one copy of the 72-base-pair repeat sequence in the SV40 promoter caused no significant decrease in CAT synthesis in monkey kidney CV-1 cells; however, an additional deletion of 50 base pairs from the second copy of the repeats reduced CAT synthesis to 11% of its level in the wild type. We also constructed a recombinant, pSV0-cat, in which the entire SV40 promoter region was removed and a unique HindIII site was substituted for the insertion of other promoter sequences.

Boshart M; Weber F; Jahn G; Dorsch-Hasler K; Fleckenstein B; Schaffner W, "A very strong enhancer is located upstream of an immediate early gene of human cytomegalovirus," Cell, (1985 Jun) 41 (2) 521-30.

A strong transcription enhancer was identified in the genomic DNA (235 kb) of human cytomegalovirus (HCMV), a ubiquitous and severe pathogen of the herpesvirus group. Cotransfection of enhancerless SV40 DNA with randomly fragmented HCMV DNA yielded two SV40-HCMV recombinant viruses that had incorporated overlapping segments of HCMV DNA to substitute for the missing SV40 enhancer. Within HCMV, these enhancer sequences are located upstream of the transcription initiation site of the major immediate-early gene, between nucleotides -118 and -524. Deletion studies with the HCMV enhancer, which harbors a variety of repeated sequence motifs, show that different subsets of this enhancer can substitute for the SV40 enhancer. The HCMV enhancer, which seems to have little cell type or species preference, is severalfold more active than the SV40 enhancer. It is the strongest enhancer we have analyzed so far, a property that makes it a useful component of eukaryotic expression vectors.

Kakutani et al., US Patent 4,988,624.

It provides a brief overview of expression and in particular at column 2 lines 13-29 points to the importance of including introns in eukaryote expression systems.

Stinski, US Patent 5,168,062.

It discloses and claims the utility of the human cytomegalovirus immediate-early promoter-regulatory DNA sequence for the regulation of heterologous gene expression.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MP Woodward whose telephone number is (703) 308-3890. The examiner can normally be reached on Monday-Thursday and alternate Fridays from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christine M. Nucker, can be reached on (703) 308-4028. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MICHAEL P. WOODWARD
PRIMARY EXAMINER
GROUP 1800

June 12, 1995